REMARKS

Claims 1-10, 13, 16-22, 27-30, 33-38 and 44-54 are pending. Claims 1, 7, 19, 30, 35, and 52 have been amended. New claims 55-72 have been added. Upon entry of the amendment, claims 1-10, 13, 16-22, 27-30, 33-38, 44-54, and 55-72 will be pending.

Support for the amendment and new claims can be found throughout the specification and the original claims. Specifically, support for the amendment to claims 1, 7, 19, 30, 35 and 52 can be found, for example, on page 9, line 4, to page 10, line 14, which indicates that a 6-mercaptopurine drug provides an active 6-mercaptopurine metabolite that has therapeutic efficacy such as 6-TG. Support for new claims 55-72 can be found, for example, in original claims 19-29 and on page 8, lines 12-32, page 17, line 25, to page 18, line 6, and page 27, line 26, to page 28, line 30. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth above the amendment to the claims in clean form as required under 37 C.F.R. § 1.121(c)(i). Applicants also attach Appendix A with marked up amendments indicated with brackets and underlining as required under 37 C.F.R. § 1.121(c)(ii).

Regarding the Information Disclosure Statement

In the previous Office Action, the Examiner indicated that the reference cited on the Information Disclosure Statement filed August 26, 1999, by Aarbackke et al. entitled "Thiopurine Biology and Pharmacology" was not made of record due to incomplete bibliographic information. The Examiner invited Applicants to submit the bibliographic information. Applicants submit herewith a new Form 1449 listing the complete bibliographic information for the Aarbaccke et al. reference, as requested by the Examiner, a copy of the reference showing the bibliographic information, and a new Information Disclosure Statement requesting that the reference be considered in the examination of the application.

Objection to the Specification

Regarding the objection to the phrase "which is incorporated herein by reference" recited on page 1, lines 5-6, Applicants respectfully request that this objection be held in abeyance until there is an indication of allowable subject matter.

Rejections Under 35 U.S.C. § 112

The rejection of claims 1-10, 13, 16-22, 27-30, 33-38 and 44-54 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicants respectfully submit that the specification provides sufficient

description and guidance to enable the claimed methods. Independent claims 1, 7, 19, 30, 35 and 52, as amended, recite administering a drug providing 6-thioguanine to a subject having an immune-mediated gastrointestinal disorder. The specification teaches methods of optimizing therapeutic efficacy and reducing toxicity for treatment of an immune-mediated gastrointestinal disorder by administering a 6-mercaptopurine drug that provides an active 6-mercaptopurine metabolite, including 6-thioguanine (page 9, line 4, to page 10, line 27; page 27, line 26, to page 28, line 30). The specification also teaches exemplary 6-mercaptopurine drugs, including 6-mercaptopurine, azathioprine, 6-methylmercaptopurine riboside and 6-thioguanine (page 9, lines 4-17). Moreover, claims 47-51 specifically recite the drugs 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside. Therefore, Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods reciting administering a drug providing 6-thioguanine. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 1, 7, 13, 16, 19, 29, 30, 35, 46 and 53 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. Regarding the phrase "wherein said drug provides 6-thioguanine to said subject," Applicants point out that this phrase has been deleted from the claims. Applicants respectfully submit that the phrase "drug providing 6-thioguanine," as recited in claims 1, 7, 19, 30, 35 and 52, as amended, is clear and definite in view of the teachings in the specification. In particular, the specification

teaches the use of a drug providing 6-thioguanine in methods of optimizing therapeutic efficacy and reducing toxicity (page 9, lines 4-17). Therefore, Applicants respectfully submit that the phrase "drug providing 6-thioguanine" is clear and definite and request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 103

The rejection of claims 1-10, 13, 16-22, 27-30, 33-38 and 44-54 under 35 U.S.C. § 103 as allegedly unpatentable over Sandborn, Scand. J. Gastroenterol. Suppl. 225:92-99 (1998) (the Sandborn reference) in view of Sandborn, U.S. Patent No. 5,733,915 (the Sandborn patent) and further in view of Berkow et al., The Merck Manual of Diagnosis and Therapy 16th ed., Merck & Co., NJ, pp. 328-330, pp. 826-828 and pp. 830-845 (1992), is respectfully traversed.

Applicants respectfully maintain that the claimed methods are unobvious over the Sandborn reference in view of the Sandborn patent and further in view of Berkow et al. The Sandborn reference, alone or in combination with the Sandborn patent and Berkow et al., does not teach or suggest Applicants' claimed methods. In particular, the combination of the Sandborn reference with the Sandborn patent and Berkow et al. does not teach or suggest the claimed methods of optimizing therapeutic efficacy and/or reducing toxicity by determining levels of the 6-mercpatopurine metabolite 6-thioguanine (6-TG) or 6-methyl-mercaptopurine (6-MMP) and indicating a need to increase or decrease the amount of drug subsequently administered if the

level is above or below a specifically recited level. Specifically, the combination of the Sandborn reference, the Sandborn patent and Berkow et al. does not teach or suggest the claimed methods of optimizing therapeutic efficacy and/or reducing toxicity by determining a level of 6-TG or 6-MMP, wherein a level of 6-TG less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of drug subsequently administered and a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs or a level of 6-MMP greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered.

To establish *prima facie* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Oryka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of the claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). In contrast, the combination of the Sandborn reference in view of the Sandborn patent and further in view of Berkow et al. does not teach or suggest all of the claim limitations. As discussed above, the combination of references does not teach or suggest the specifically recited levels of 6-TG and/or 6-MMP indicating a need to increase or decrease the amount of drug subsequently administered. Absent such a teaching or suggestion, Applicants respectfully submit that the claimed methods are unobvious over the Sandborn reference in view of the Sandborn patent and further in view of Berkow et al.

Furthermore, Applicants respectfully submit that there was skepticism in the field of gastroenterology and inflammatory bowel disease that the levels of 6-mercaptopurine metabolites recited in the claims would have been predictive for optimizing therapeutic efficacy and/or minimizing toxicity. As evidence of skepticism in the field, Applicants submit herewith a Rule 132 Declaration (Exhibit 1) by Dr. Stephan Targan, an expert in the field of gastroenterology and inflammatory bowel disease, attesting to his belief that there was skepticism expressed by experts in the field of gastroenterology and inflammatory bowel disease that the recited levels of 6-mercaptopurine metabolites would have been predictive of therapeutic efficacy or reduced toxicity.

Also submitted herewith is a reference by Sandborn et al., Gastroenterology 117:527-535 (1999) (Exhibit A), of which Dr. Targan is a co-author, which indicates that a red blood cell 6-TG concentration of ≥200 pmol/$8x10^8$ RBCs was not found to be associated with greater likelihood of response (see page 531, first column, last sentence; and page 533, second column, last paragraph). Regarding toxicity, the Sandborn et al. reference also indicates that the authors were unable to identify a cutoff value for the RBC 6-TG concentration that accurately predicted leukopenia (page 534, first column, first complete paragraph). The Sandborn et al. reference was submitted for review in January of 1999 and was published in September of 1999, and Applicants therefore submit that the reference provides supportive evidence that there was skepticism by experts in the field around the time the application was filed, September of 1998 and April of 1999,

that the specifically recited levels of 6-TG would have been predictive of therapeutic efficacy or reduced toxicity.

Applicants also submit herewith a reference by Belaiche et al., Scand. J. Gastroenterol. 36:71-76 (2001)(Exhibit 2), which further corroborates Applicants' assertion that there was skepticism by experts in the field that the levels of 6-mercaptopurine metabolites specifically recited in the claims would have been predictive of therapeutic efficacy. In particular, Belaiche et al. found no significant correlation between RBC 6-TG concentrations and various biological parameters tested except for the mean erythrocyte volume (see abstract). The median 6-TG concentration was found to be similar in the three groups categorized (page 73, column 2, second paragraph of "Results"), including two groups having patients exhibiting quiescent Crohn's disease (CD) and one group having active symptomatic CD (page 72, column 2, and Table II). In addition to finding no significant difference in 6-TG levels between the groups, Belaiche et al. reports no significant correlation between 6-TG concentration and various biological parameters except mean erythrocyte volume, including leukocyte count, neutrophil count, relative neutrophilia, lymphocyte count and relative lymphocytosis (page 73, column 2, second paragraph of "Results" and Table III). Accordingly, Applicants respectfully submit that Belaiche et al. corroborates Applicants' assertion that there was skepticism in the field that the specifically recited levels of 6-mercaptopurine metabolites would have been predictive of therapeutic efficacy.

Regarding the specifically recited level of 6-MMP, the Sandborn patent, U.S. Patent No. 5,733,915, describes a lack of correlation between RBC 6-MMP levels and a change in the Crohn's disease activity index (CDAI) (column 7, lines 61-67). The lack of correlation was seen at 4, 8 and 16 weeks and was similarly observed for 6-TG. Accordingly, Applicants respectfully submit that the Sandborn patent corroborates Applicants' assertion that there was skepticism in the field that the specifically recited levels of 6-mercaptopurine metabolites would have been predictive of therapeutic efficacy.

In contrast to the skepticism exhibited by some experts, the methods of the invention have been successfully commercialized. In particular, Prometheus Laboratories, Inc., the licensee of the above-identified application, has successfully commercialized the assay of determining 6-thioguanine and 6-methyl-mercaptopurine in red blood cells for optimizing therapeutic efficacy and/or reducing toxicity. Year-to-date for 2001, over 600 tests per month have been performed.

In conclusion, Applicants respectfully submit that the combination of the Sandborn reference in view of the Sandborn patent and further in view of Berkow et al. does not teach every limitation of the claims and therefore cannot render the claimed methods obvious. Furthermore, Applicants respectfully submit that there was skepticism in the field of gastroenterology and inflammatory bowel disease that the specifically recited levels of 6-mercaptopurine metabolites were predictive of therapeutic

efficacy and/or reduced toxicity. Therefore, Applicants respectfully submit that the claimed methods are unobvious over the Sandborn reference in view of the Sandborn patent and further in view of Berkow et al. and respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

July 2, 2001
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